HEPATITIS C:
THE END OF THE BEGINNING
AND PERHAPS THE BEGINNING OF THE END

FINANCIAL DISCLOSURE

People who work at NIH only dream about having financial disclosures

Wait, this just in …….

NIH has just prohibited dreaming

CRITICAL NON-FINANCIAL DISCLOSURES

- My guiding scientific principle is that to steal from one is plagiarism……..

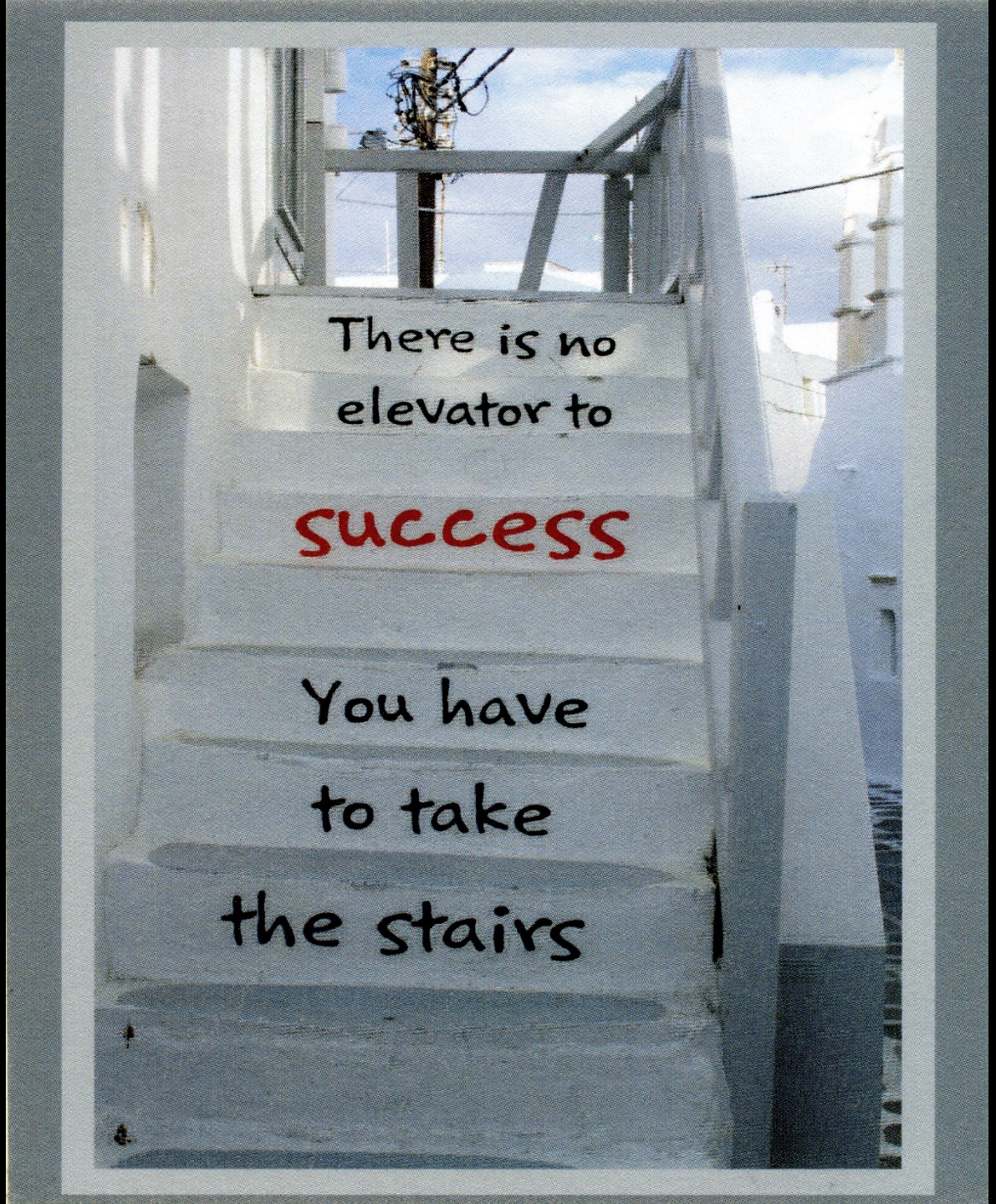
  but to steal from many is research

- Nothing I say reflects the position of the US government ----

  which instantly gives it great credibility and relevance

- My memory is not as sharp as it used to be

- And also, my memory is not as sharp as it used to be


There is no
elevator to
success
You have
to take
the stairs

TIMELINE OF HEPATITIS HISTORY

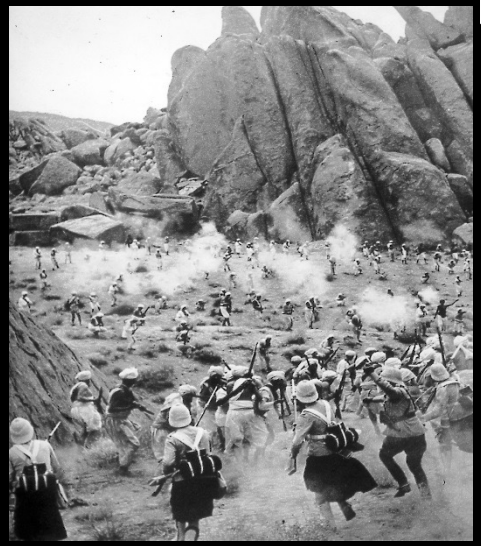
First to Describe:

- Ikterus
- Kirros

425-350 BC

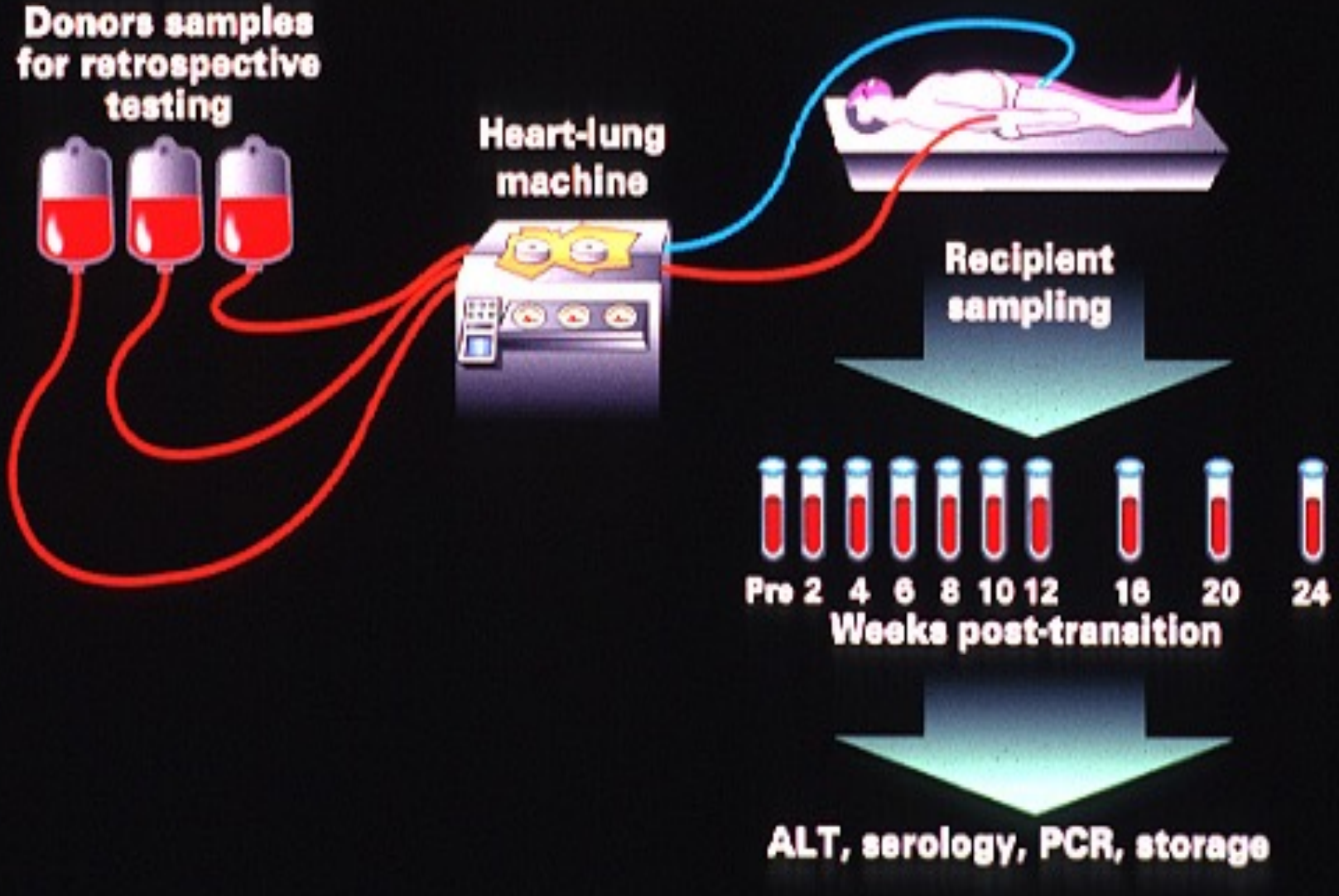
Campaign jaundice
Vaccine jaundice
Hep A vs. Hep B

2000 YEARS

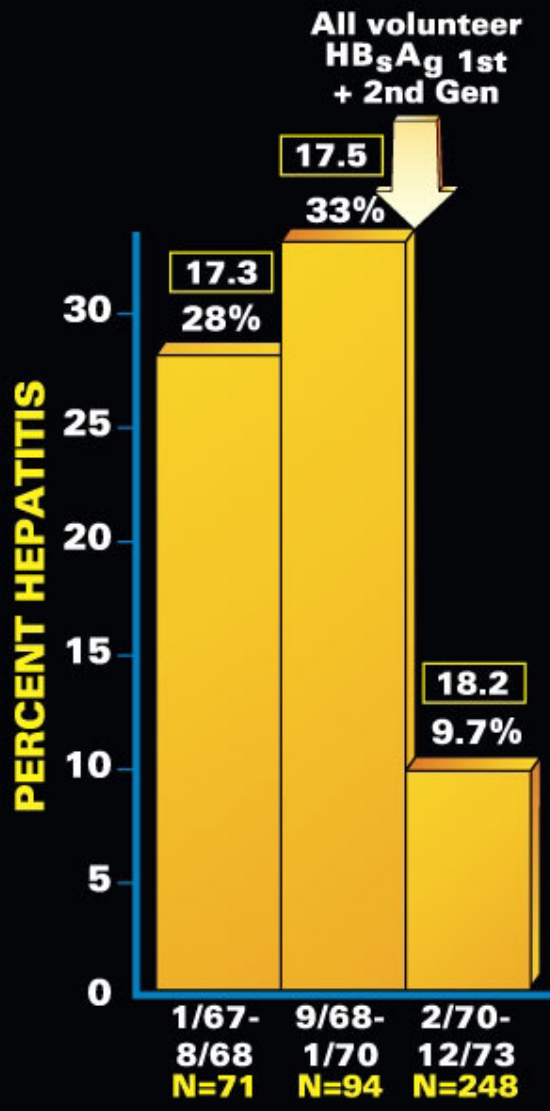


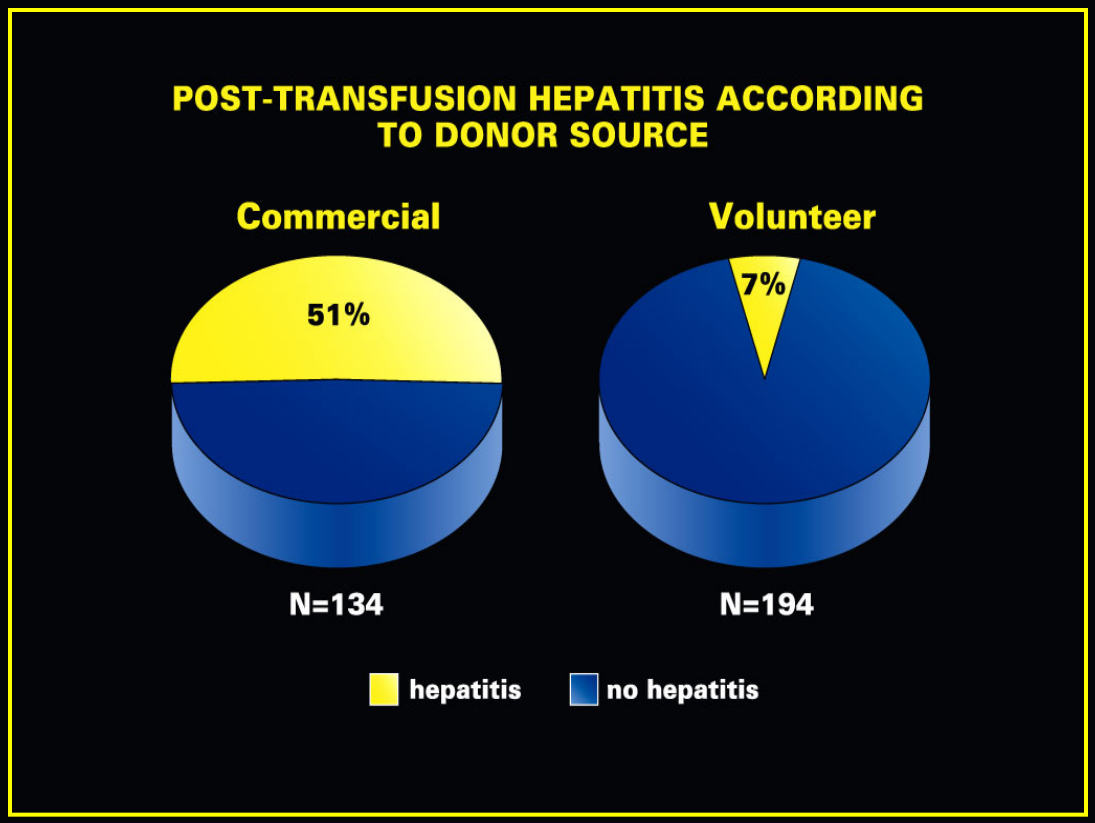
1960's

STUDY DESIGN: NIH PROSPECTIVE STUDIES OF TRANSFUSION-ASSOCIATED HEPATITIS

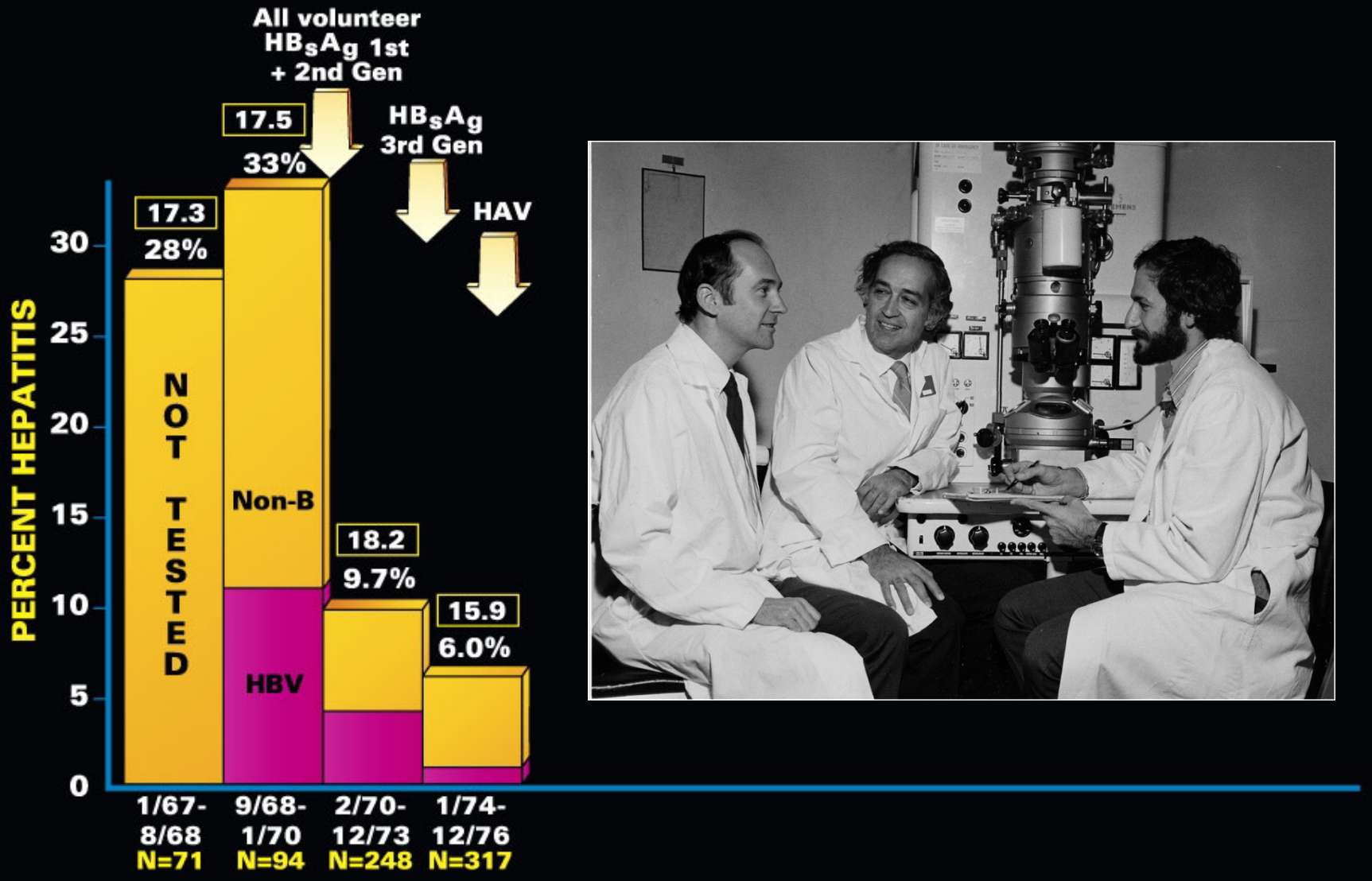


Post-Transfusion Hepatitis at NIH-1

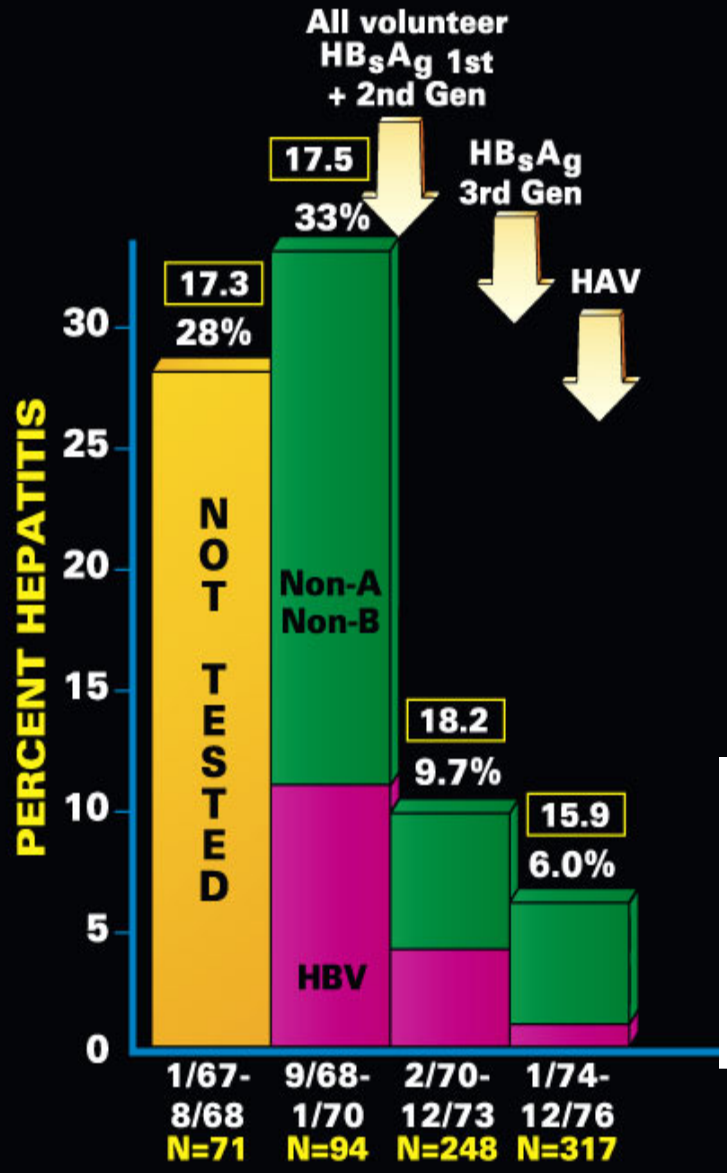




Post-Transfusion Hepatitis at NIH-2



Post-Transfusion Hepatitis at NIH-3



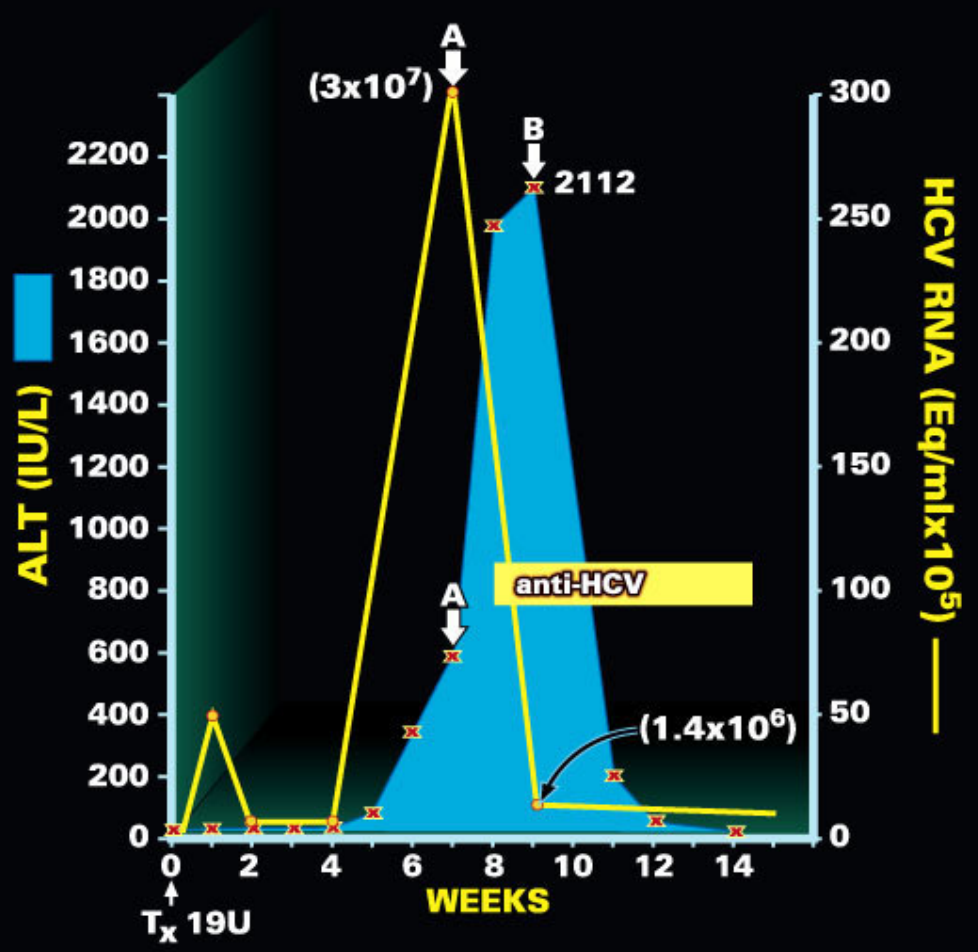
Transmitted From

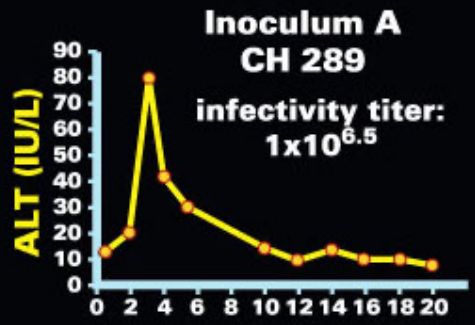
- Patients with acute and chronic NANB hepatitis
- Asymptomatic implicated donors

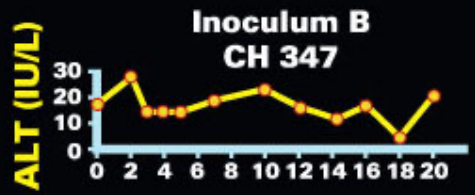
I ALWAYS GIVE 100%
AT WORK

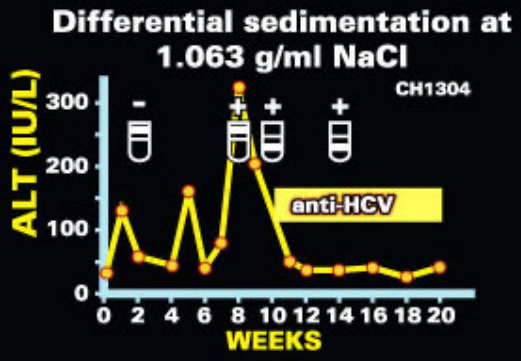
12% on Monday
23% on Tuesday
37% on Wednesday
23% on Thursday
5% on Friday

HEPATITIS C TRANSMISSION VS. VIRAL LOAD AND ANTIBODY RESPONSE IN PATIENT H

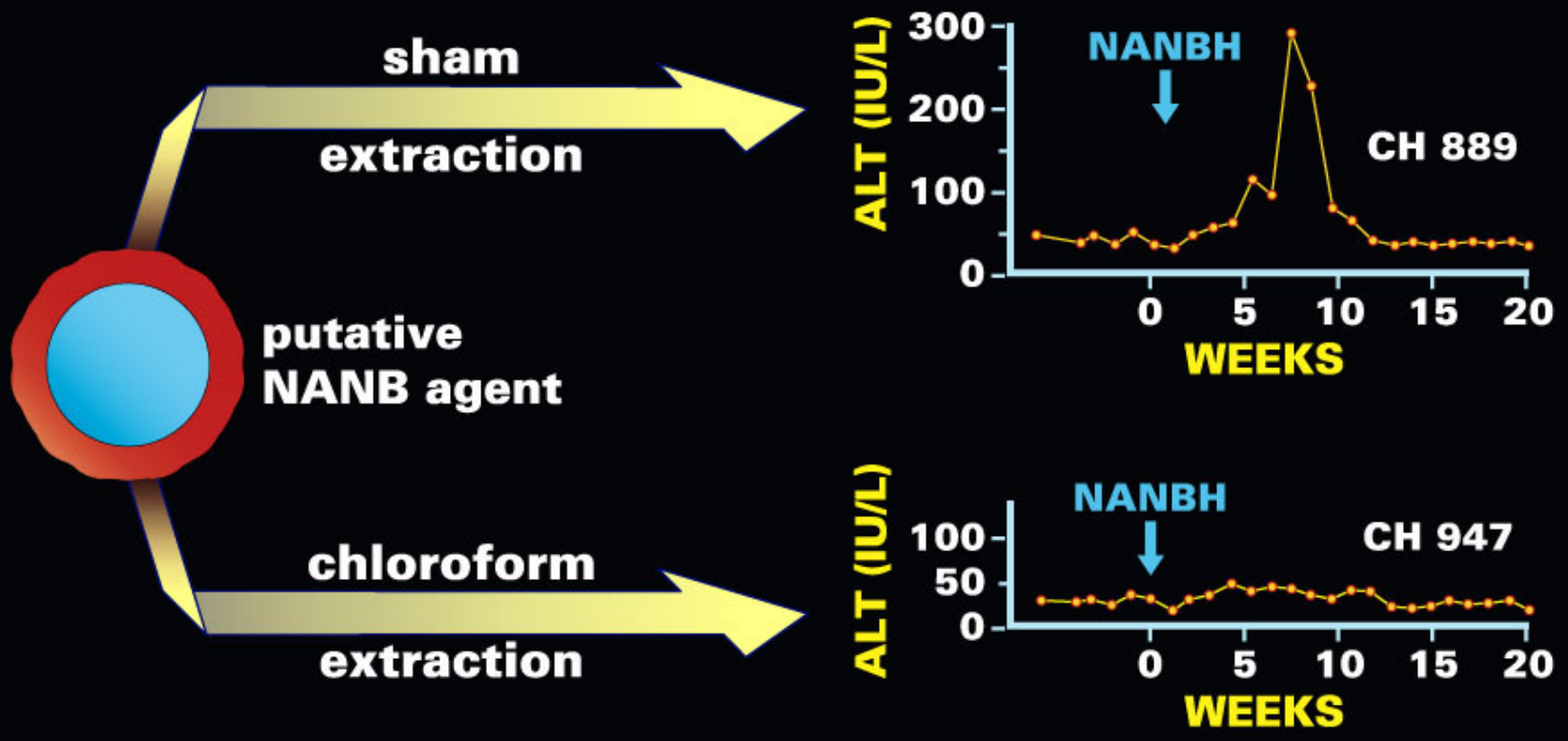






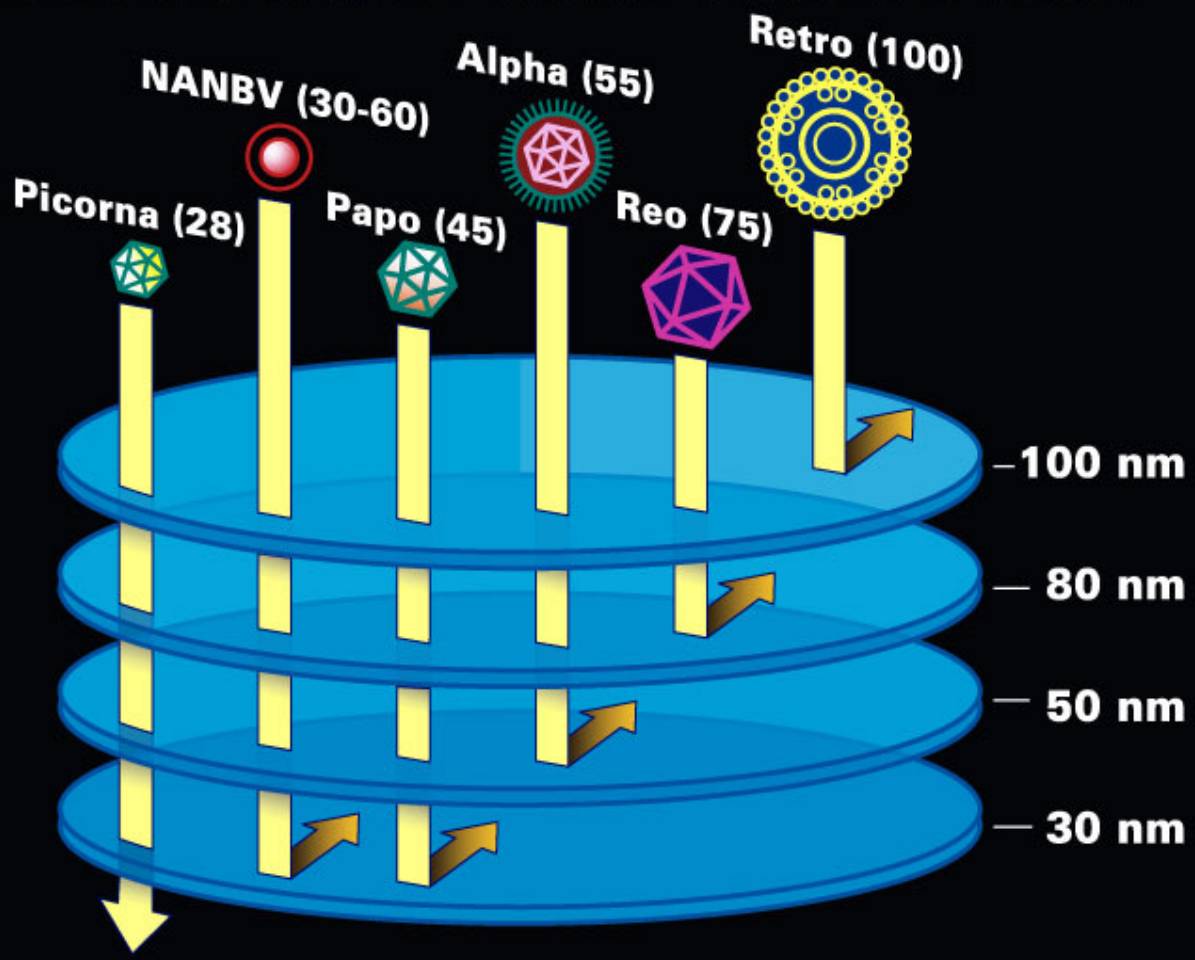


CHLOROFORM EXTRACTION OF H'77 NON-A, NON-B INOCULUM

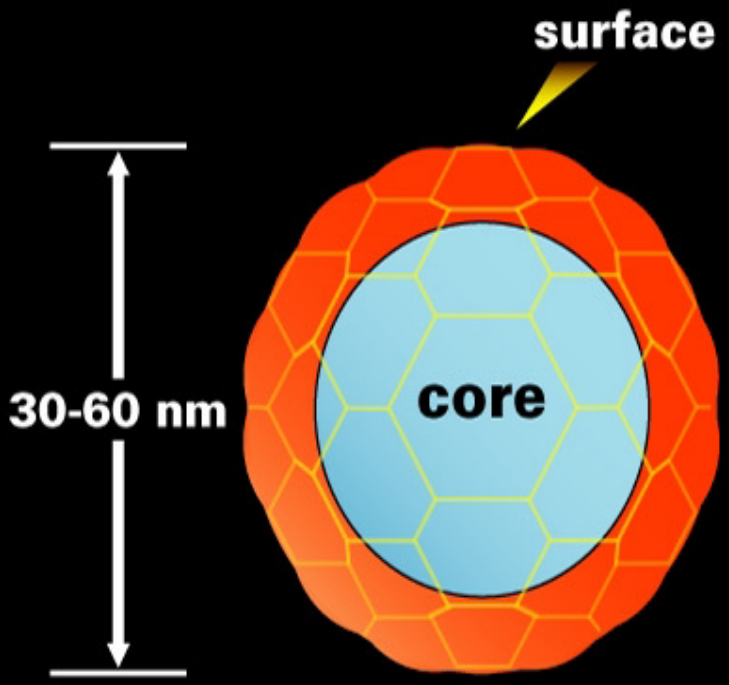


Feinstone, et al Infection & Immunity 1983; 41: 816

SIZE DETERMINATION OF NANBV BY FILTRATION AND CHIMP INOCULATION



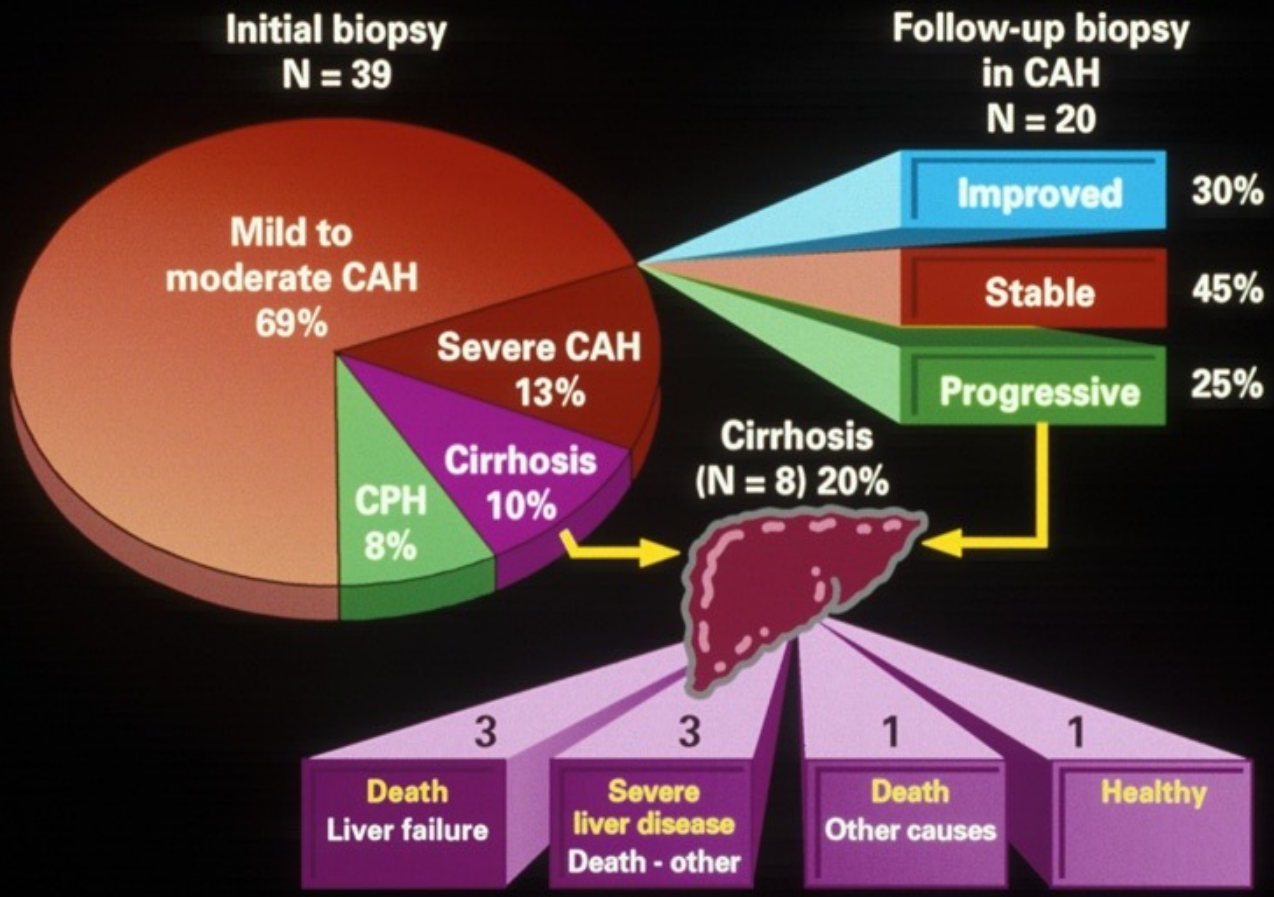
PUTATIVE STRUCTURE OF THE TUBLAR FORMING NON-A, NON-B HEPATITIS AGENT



Candidate viruses

- alphaviruses (RNA)
- flaviviruses (RNA)
- hepadna viruses (DNA)
- delta virus (RNA)
- new viral class

Histologic Diagnosis and Outcome in Transfusion-Associated Hepatitis C



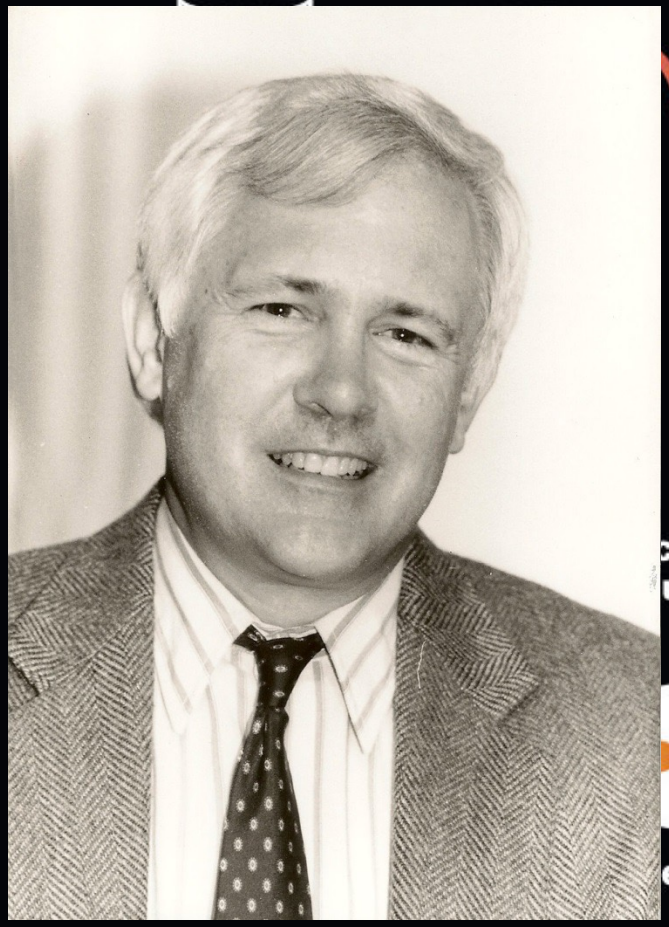
While the clinical severity of NANBH became increasingly evident over the next decade, no serologic, enzymatic, radioimmunologic or early molecular method led to a specific NANB assay or further elucidated the nature of the agent.

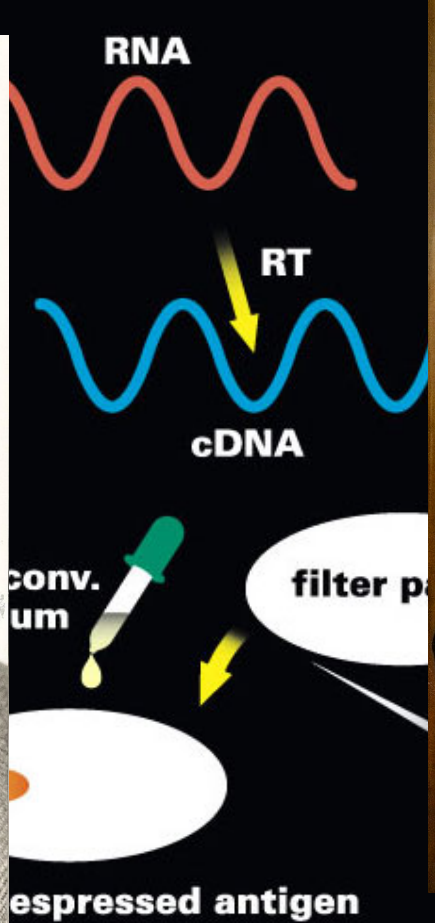
A POEM OF FRUSTRATION

"I Can't See The Forest

For The HB Ags"

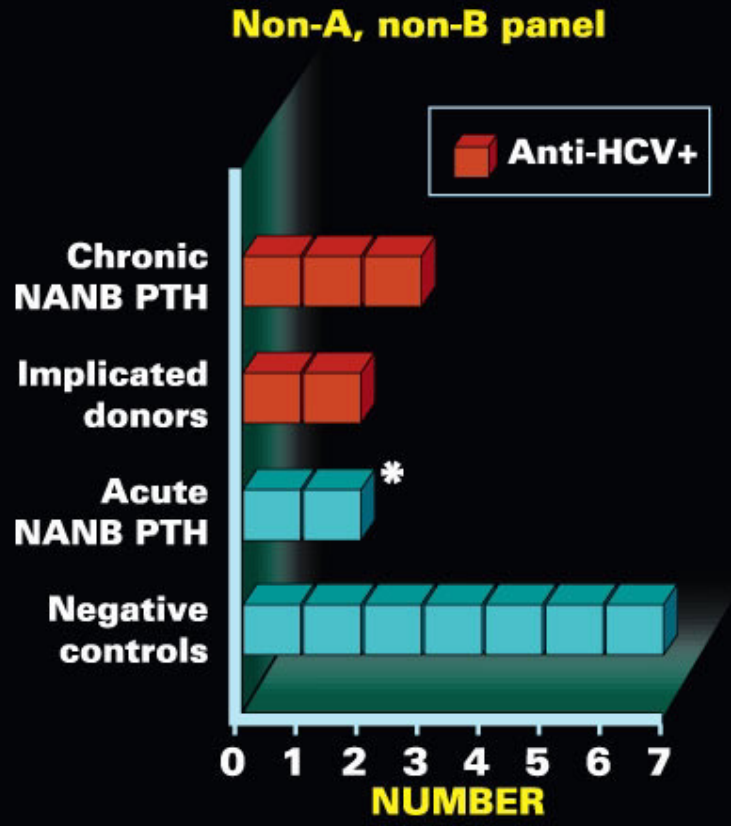
CLONING OF NANB AGENT IN GT-11 EXPRESSION VECTOR

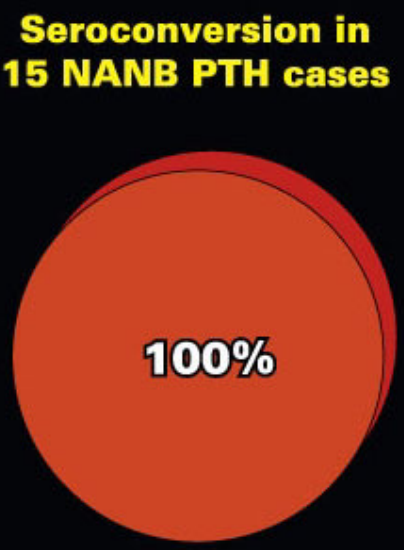


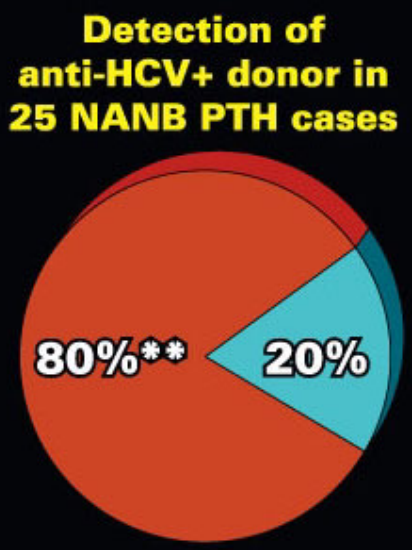


agar

VALIDATION OF THE CHIRON DISCOVERY FOR THE DETECTION OF NANB/HCV INFECTION



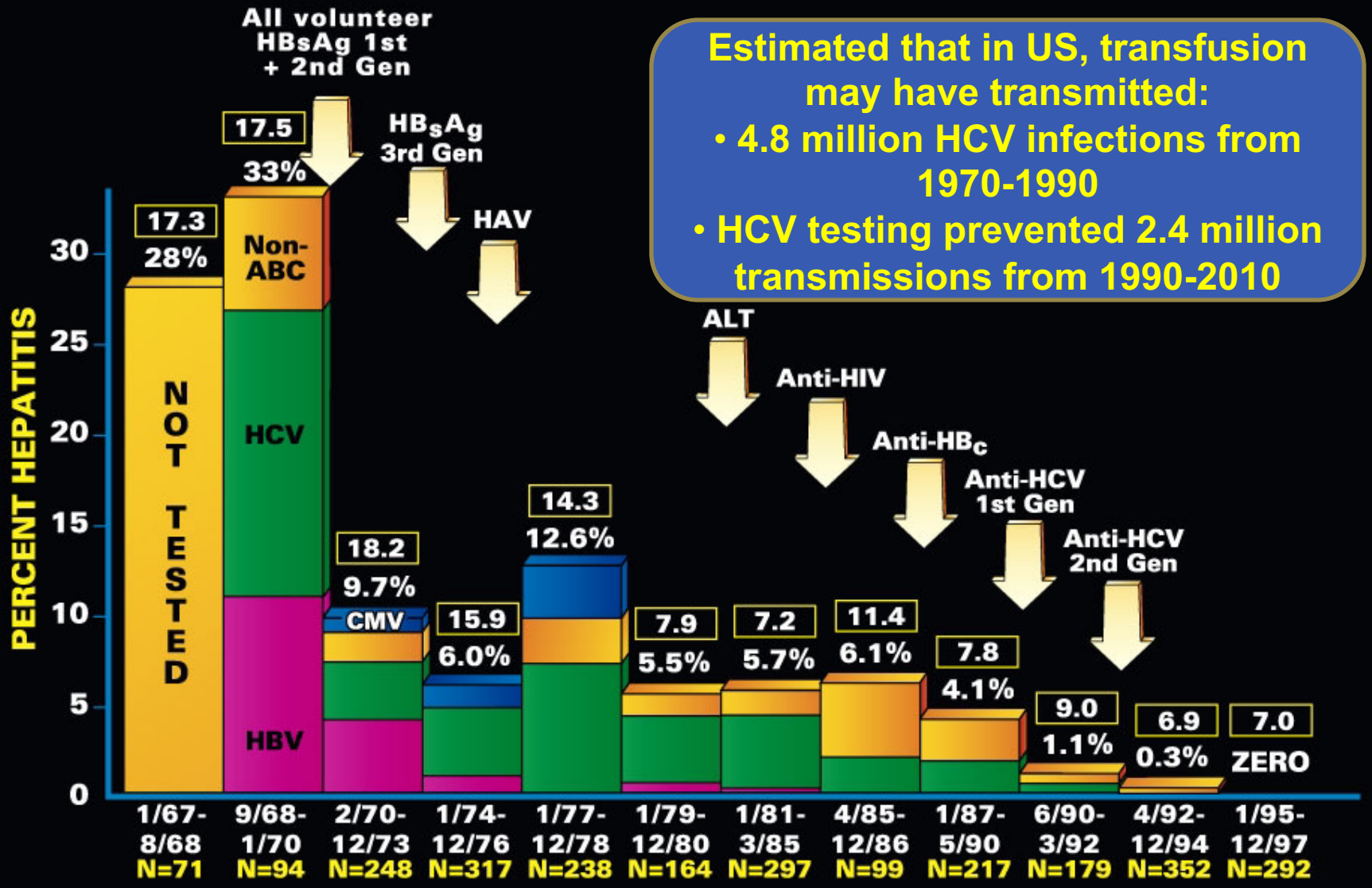




*Subsequent seroconversion

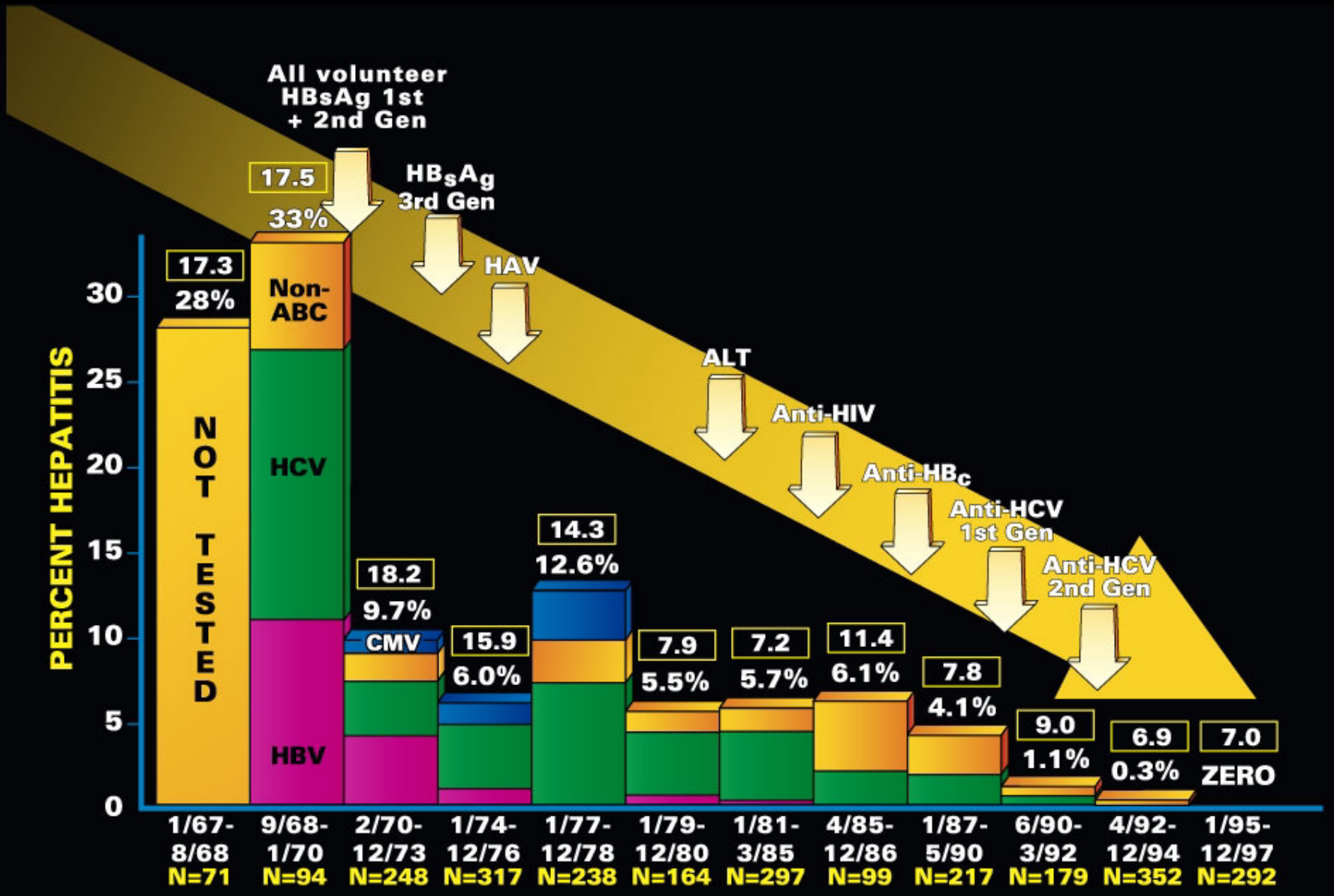
**88% with 2nd gen. assay

Post-Transfusion Hepatitis at NIH-5

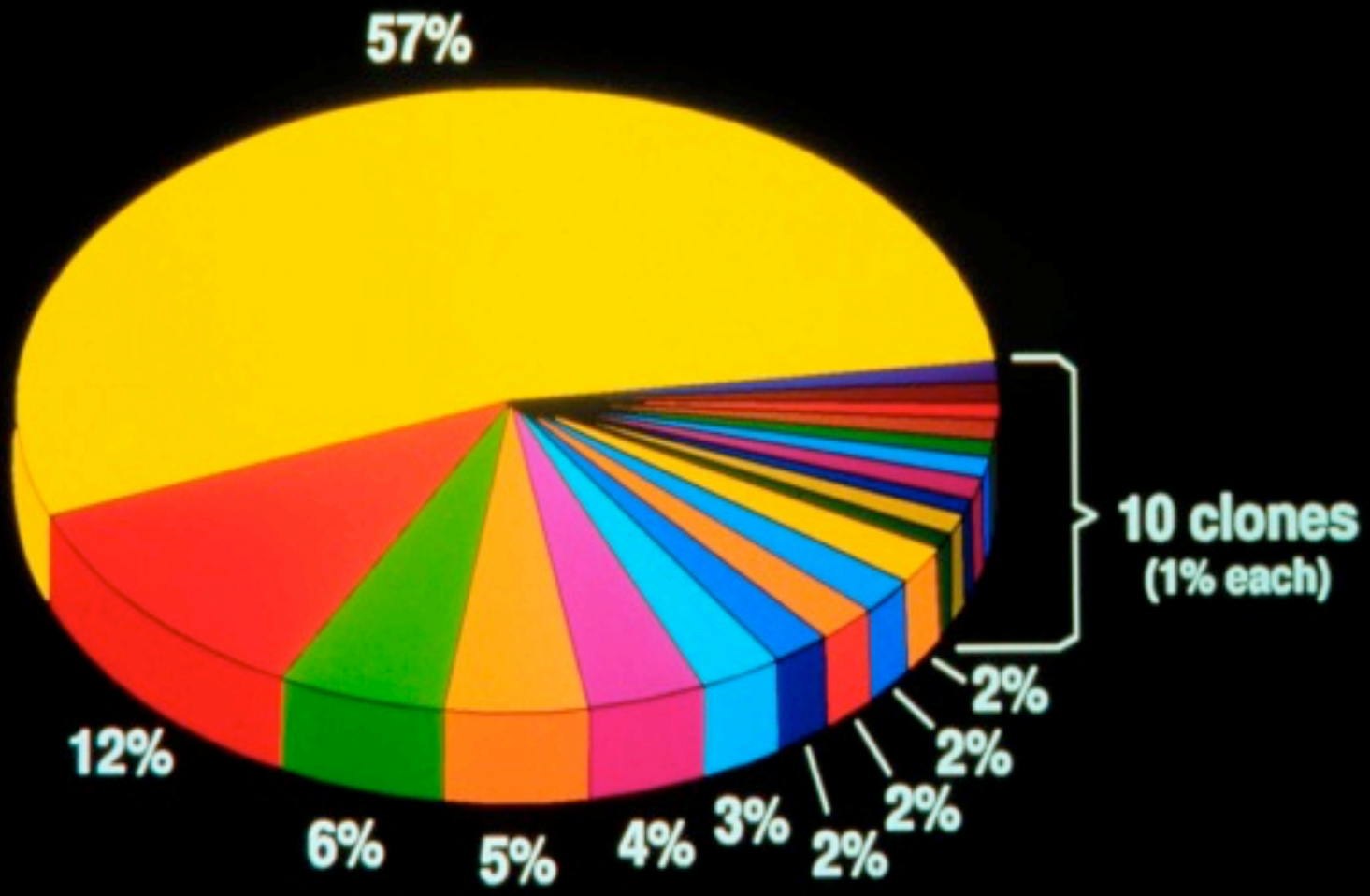


Estimated that in US, transfusion may have transmitted:

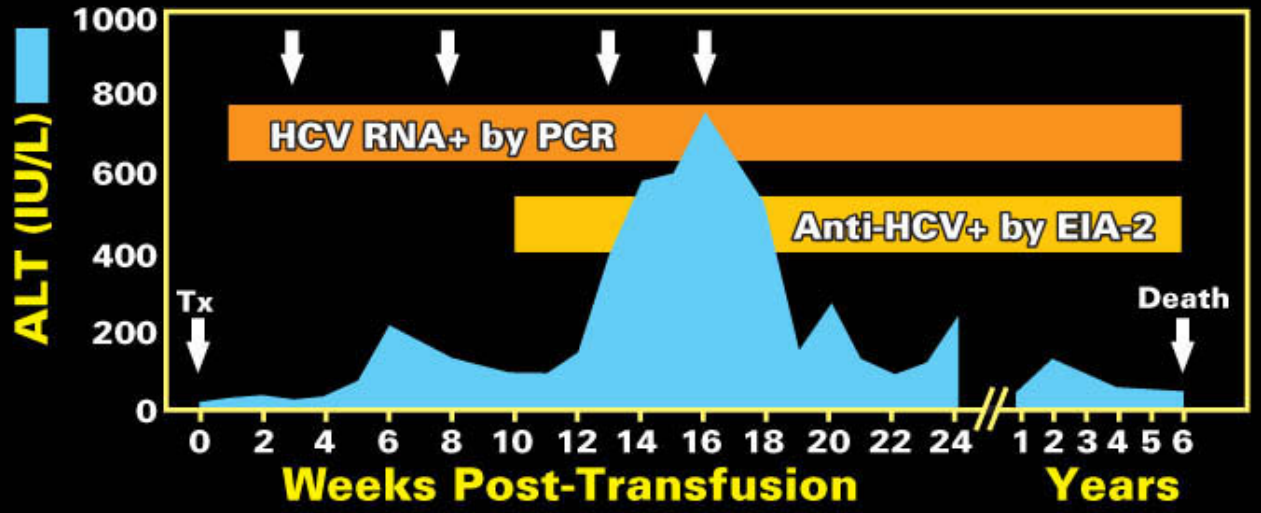
- **4.8 million HCV infections from 1970-1990**
- **HCV testing prevented 2.4 million transmissions from 1990-2010**


All volunteer HBsAg 1st + 2nd Gen
HBsAg 3rd Gen
HAV
ALT
Anti-HIV
Anti-HBc
Anti-HCV 1st Gen
Anti-HCV 2nd Gen
PERCENT HEPATITIS
30
25
20
15
10
5
0
17.3
28%
NOT TESTED
17.5
33%
Non-ABC
HCV
HBV
18.2
9.7%
CMV
15.9
6.0%
14.3
12.6%
7.9
5.5%
7.2
5.7%
11.4
6.1%
7.8
4.1%
9.0
1.1%
6.9
0.3%
7.0
ZERO
1/67-8/68 N=71
9/68-1/70 N=94
2/70-12/73 N=248
1/74-12/76 N=317
1/77-12/78 N=238
1/79-12/80 N=164
1/81-3/85 N=297
4/85-12/86 N=99
1/87-5/90 N=217
6/90-3/92 N=179
4/92-12/94 N=352
1/95-12/97 N=292

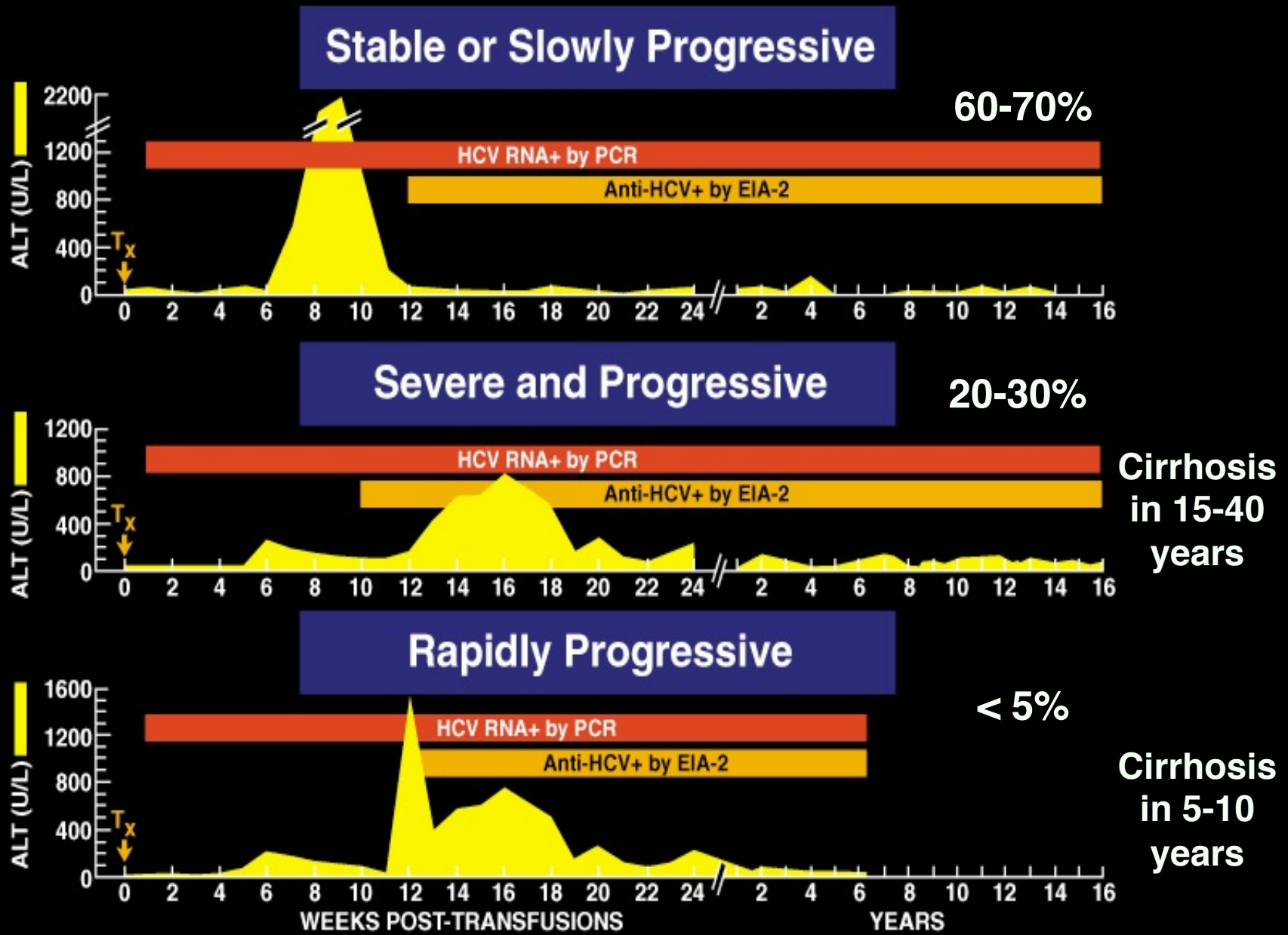
Quasispecies Nature of HCV, Strain H77
Analysis of HVR1 Region from 105 Clones



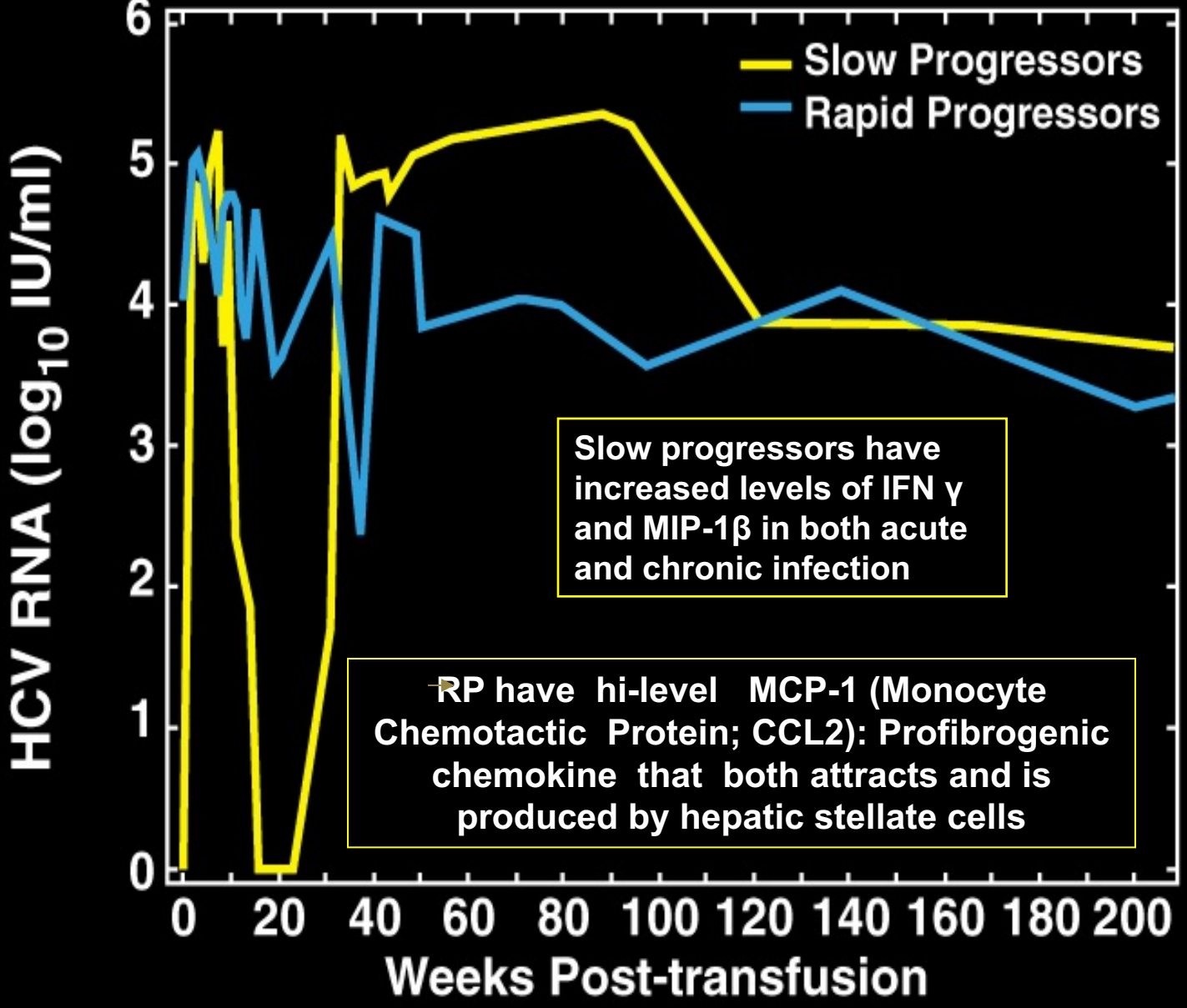
EVOLUTION OF HCV QUASISPECIES IN A PATIENT WITH RAPIDLY PROGRESSIVE CHRONIC HEPATITIS C



Outcome of Chronic HCV Infection in Transfusion-Associated Hepatitis C

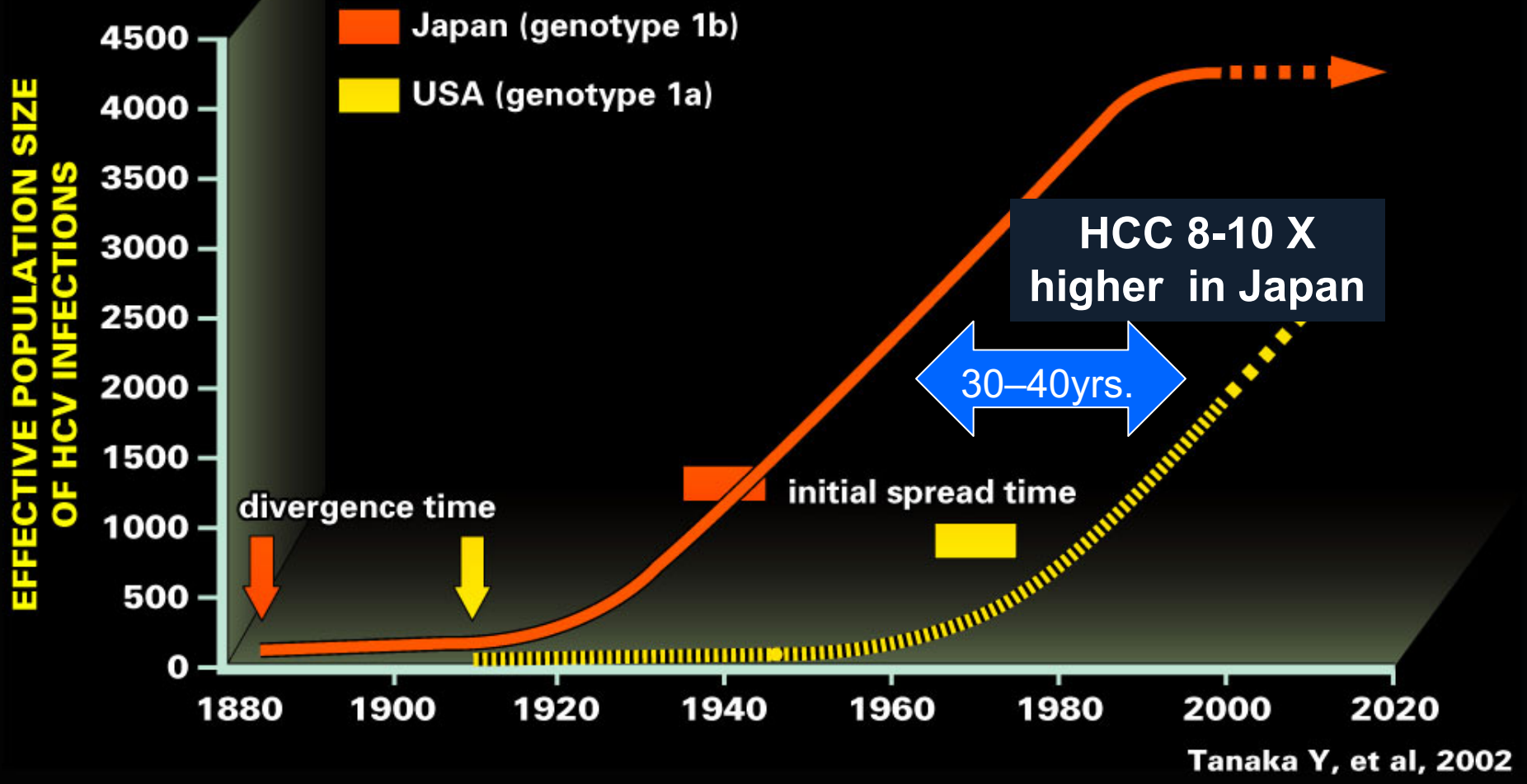


Slow vs. Rapid HCV Progressors: Viral Load

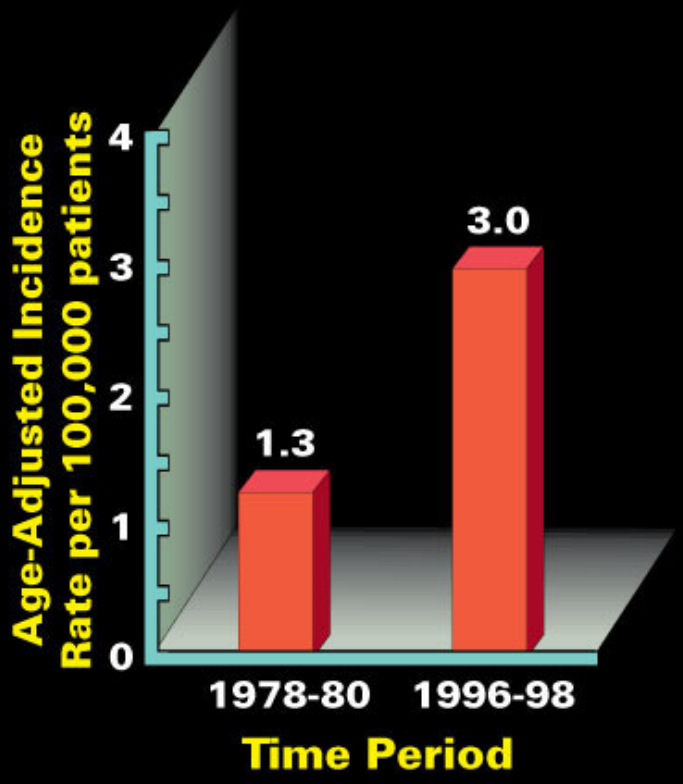


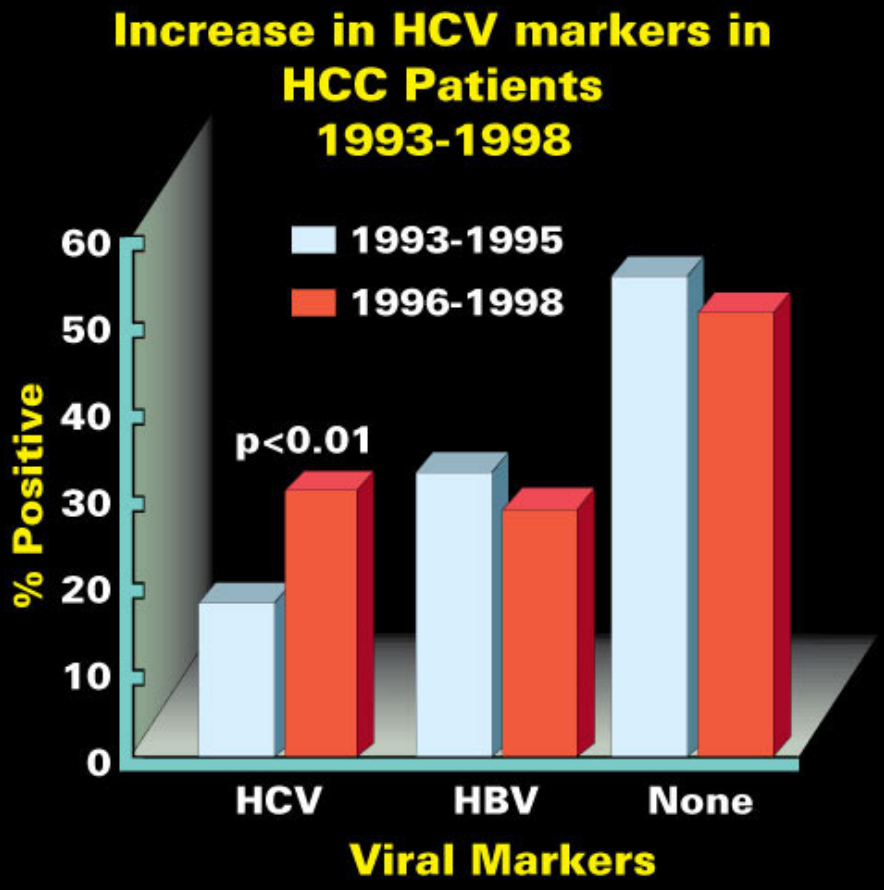
Farci P, et al: PNAS 2012;109:14562

MOLECULAR CLOCK OF HCV GENOTYPE 1 EVOLUTION IN JAPAN AND THE USA



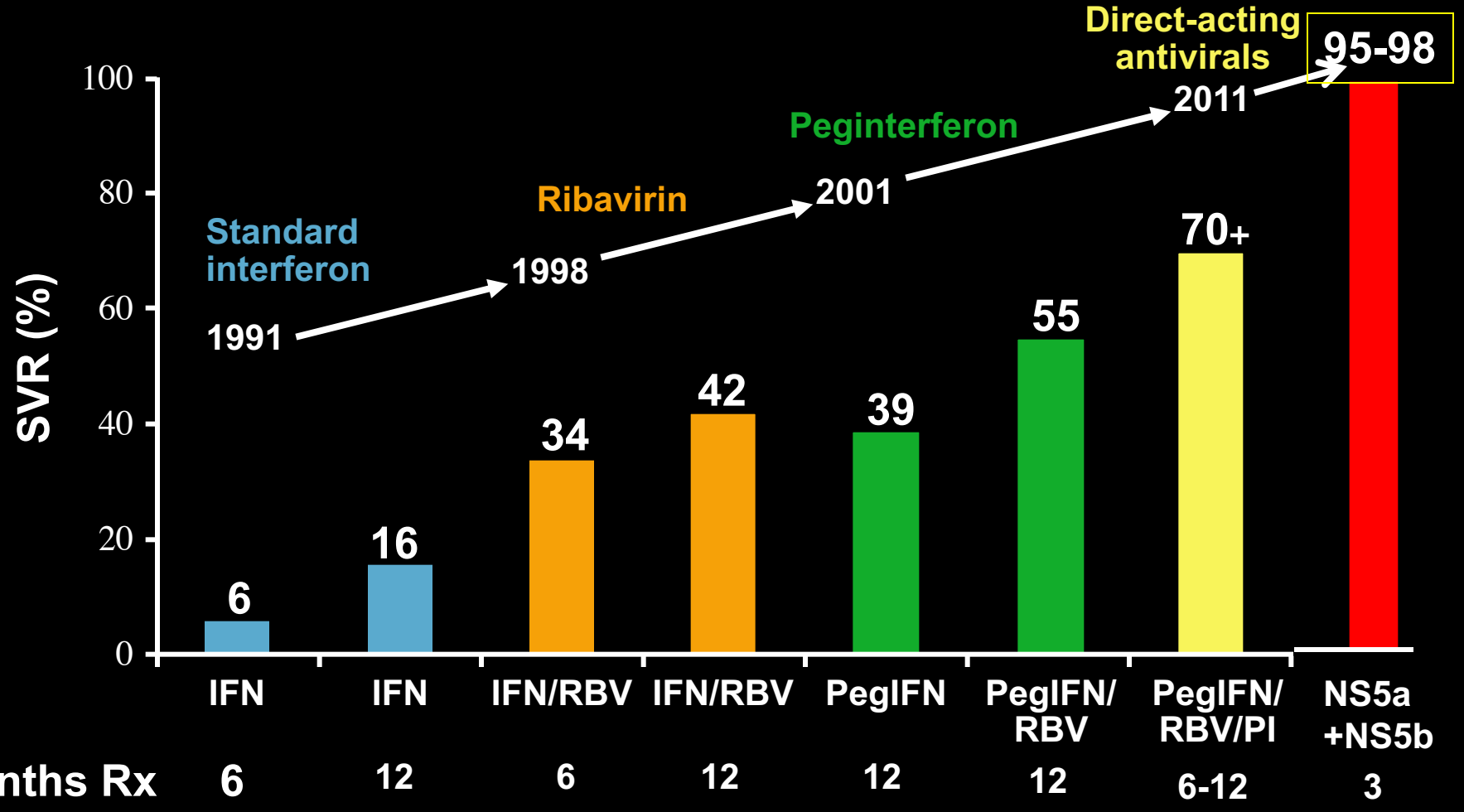
RISING INCIDENCE OF HCC IN THE UNITED STATES





Assuming no changes in standard of care, the total number of patients with advanced liver disease/HCC by 2029 projected to be > 4-fold higher than in 2009

Milestones in Therapy of Gt 1 HCV



HCV: THE FUTURE
THE GLASS IS HALF-FULL

With cure rates approaching 100%, from this time forward, once HCV infection is identified, no one should develop cirrhosis or die from hepatitis C sequelae

THE GLASS IS HALF-EMPTY
HURDLES TO HEPATITS C ERADICATION

Identification of cases:

Estimated that 50% of HCV infections remain unidentified; much higher in developing world; enhanced population screening is priority one

Access to Treatment:

Even among known carriers, only a minority get treated with DAAs, though the proportion treated is increasing

High cost of Drugs:

Cost is the main impediment to treatment preventing the cure of millions. Cure is no longer constrained by science, but is a matter of dollars

Can HBV and HCV Infections be Eradicated ?

HBV → Vaccine >95% Eff. / Nucleot(s)ide Tx

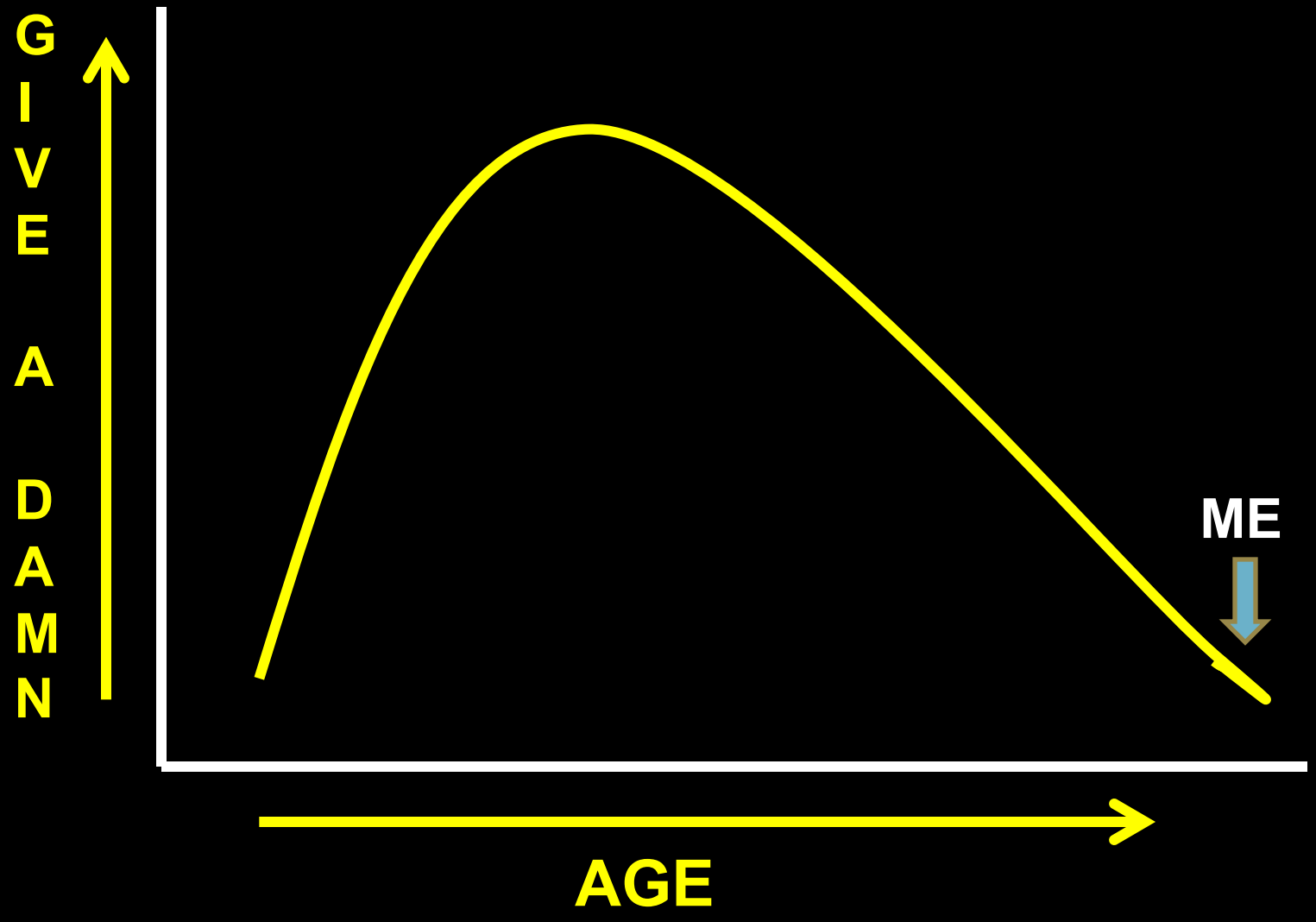
HCV → DAA >95% cure

And then a miracle occurs

GLOBAL ERADICATION

- Universal vaccination HBV
- Detection of almost all HCV carriers through massive global screening
- global delivery of DAAs with >90% penetration in each population
- The political, corporate, philanthropic and moral will to make it happen

A PHILOSOPHIC PERSEPECTIVE OF LIFE VERSUS AGE



I NEVER HAD NO

NOBEL DREAMS